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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,999	03/01/2002	Takashi Kawasuji	2002_0288A	5732

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
02/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/069,999	KAWASUJI ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-14 and 17-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *7-14* is/are allowed.

6)☒ Claim(s) *17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered. Claims 7-14 and 17-23 were pending. Applicants amended claims 7 and 9. No claims were added or canceled. Therefore, claims 7-14 and 17-23 currently still pending.

2. Claims 7-14 are allowable. Claims 17-23, previously withdrawn from consideration as a result of a restriction requirement, require all the limitations of an allowable claim. Pursuant to the procedures set forth in MPEP § 821.04(a), the restriction requirement among inventions I-IV, as set forth in the Office action mailed on 6/23/05, is hereby withdrawn and claims 17-23 are hereby rejoined and fully examined for patentability under 37 CFR 1.104. In view of the withdrawal of the restriction requirement, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Thus, claims 7-14 and 17-23 are examined on the merits.

3. Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

4. The 35 U.S.C. § 112, second paragraph rejection denoted "A" is withdrawn in view of Applicants amendments to claim 7. The New Matter rejection denoted "A" is withdrawn in view of Applicants' amendments to claim 7. The objection to claims 12 and 14 is withdrawn in view of Applicants' amendments to claim 7.

New Rejections

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 17-23 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicant's claimed invention is directed to pharmaceutical compositions, medical mixtures and methods for treating diseases like AIDS and AIDS-related complications caused by HIV and other antiviral agents using the integrase inhibitors described in claims 7-14. However, the claimed scope is broad enough to encompass pharmaceutical compositions and methods for treating viruses that do not possess an integrase enzyme activity (e.g., see claim 18 wherein anti-viral agents are claimed in general, not just retroviruses). According to Flint et al., most families of viruses do not employ the use of an integrase enzyme for replication (see Flint, Enquist, Krug, Racaniello and Skalka, "Principles of Virology" ASM press, 2000, pages 750-780; see especially page 764, step 4 wherein the integrase step is shown; compare to the other classes of viruses where no integrase activity is shown such as the picoviruses set forth on pages 750-752 wherein a (-) RNA strand serves as a template for the production of (+) RNA strands without the use of an integrase for replication).

In contrast, the specification does not set forth any examples of compositions or any methods for treating viral diseases. The specification only states that the claimed compounds can be used as inhibitors of HIV-1 integrase (e.g., see specification, pages 138 and 140). No in vivo data has been provided whatsoever. Furthermore, Applicants provide no guidance for treating other families of viruses such a picornaviruses, togaviruses, etc. that do not rely on an integrase enzyme for replication (see above).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52,

196 USPQ 465, 46 (CCPA 1978); see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). The "written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" (e.g., see *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the genus encompasses many different viruses that do not replicate by the same mechanism and, in particular, do not employ an integrase enzyme (e.g., see Flint, Enquist, Krug, Racaniello and Skalka, "Principles of Virology" ASM press, 2000, pages 750-780; compare retroviruses to other classes set forth therein). Consequently, the HIV-1 retrovirus is not "representative" of these other classes. That is, a person of skill in the art would not expect an integrase inhibitor to have any effect on the vast majority of known viruses since these viruses do not employ an integrase enzyme in their replication cycles (see Flint et al, pages 750-780 wherein replication cycles for various classes of viruses are set forth; however, only retrovirus use integrase enzymes for replication). Thus, Applicants were not in possession of compositions and methods for treating this broad array of causative agents.

In addition, it is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies, as taught by Fahey et al. (Fahey et al., "Status of immune based therapies in HIV infection and AIDS", *Clin. exp. Immunol.* **1992**, *88*, 1-5). The obstacles to therapy of HIV are well documented in

the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed pharmaceutical compositions and vaccines to treat infection.

Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment of HIV infection. For example, Fahey et al. discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). This is further evidenced by the teachings of Stein et al. which states that rational development of HIV therapeutics "is limited by our current knowledge of their mechanisms and effects and of the immune system's complex and overlapping activities" (see Stein et al., CID, Vol. 17, 749-771 (1993), page 765, last paragraph). Particularly relevant to the claimed integrase inhibitors, Nair et al. state, "There are no drugs for HIV/AIDS in clinical use where the mechanism of action is inhibition of HIV integrase" (e.g., see Nair, "HIV integrase as a target for antiviral chemotherapy" Reviews in medical

Virology 2002, 12, pages 179-193, especially page 179, column 2, noting that HIV integrase "has received much less consideration" than other potential targets such as HIV reverse transcriptase and HIV protease). In addition, Tramontano et al. in vitro results don't correlate well with in vivo results for integrase inhibitors (e.g., see Tramontano et al., *Biochemical Pharmacology* **2004**, *67*, 1751-1761, especially page 1752, first full paragraph, "Since integration is an essential requirement for the HIV-1 replication, IN is considered an attractive target for the development of new antiviral therapies ... However, with few exception, the rIN inhibitors identified ... rarely prove to be able to block both the virus replication in cell-bassed assays and the DNA integration in PIC-based assays ...The striking lack of correlation between the in vitro and in vivo activity of the large majority of anti-IN compounds, irrespectively of the chemical class to which they belong to [4] most likely reflects the inadequacy of the cell-free assays to reproduce the cellular integration process"). Thus, it is clear that the vast majority of integrase inhibitors do not work as therapeutics and, as of Applicants' filing date, there was no reliable way to test their efficacy.

Also, a person of skill in the art would not expect an HIV-1 integrase inhibitor to work on an HIV-2 integrase or, alternatively, some other class of retrovirus enzyme. Although, molecules like LEDGF that bind more than one type are known (i.e., HIV-1, HIV-2, etc.), this represents the exception rather than the rule (e.g., see Cherepanov et al., Solution structure of the HIV-1 integrase-binding domain in LEDGF/p75, pages 526-532, especially page 520, column 2, last paragraph, "It seems that binding to LEDGF is conserved among the Lentiviridae subfamily of retroviruses and has so far been

demonstrated for HIV-1, HIV-2, and FIV INs. In contrast, two other well studied IN-binding partners, integrase-interactor 1 and uracil DNA glycosylase 2 (UNG2), seem HIV-1-specific [i.e., do not react with HIV-2, etc.]." Thus, a person of skill in the art wouldn't expect an HIV-1 integrase inhibitor to inhibit a wide class of viral integrase enzymes because each enzyme possesses a different structure. Thus, it is clear that Applicants were not in possession of methods and compositions for treating a narrower subgenus of retroviruses, HIV or even HIV-1 itself.

Finally, the art of making the claimed salts and hydrates is also unpredictable with respect to pharmaceutical compositions and their methods of use. See for example US Patent No. 6,864,244 column 1 - column 2; which states: "Salts of acidic and basic compounds can alter or improve the physical properties of the parent compound. These salt forming agents, however, must be identified empirically by the pharmaceutical chemist since there is no reliable method to predict the influence of a salt species on the behavior of a parent compound in dosage forms. Effective screening techniques, which potentially could simplify the selection process, are unfortunately absent"). Thus, Applicants were not in possession of the claimed salts, hydrates, etc. either even if, assuming arguendo, it could be proved that the claimed integrase inhibitors could be used in a therapeutically meaningful way at the time of filing.

6. Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for inhibiting HIV-1 integrase, does not reasonably provide enablement for "pharmaceutical" compositions and methods of treating

diseases such as AIDS and AIDS-related compositions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicant's claimed invention is directed to pharmaceutical compositions, medical mixtures and methods for treating diseases like AIDS and AIDS-related complications caused by HIV and other antiviral agents using the integrase inhibitors described in claims 7-14. However, the claimed scope is broad enough to encompass pharmaceutical compositions and methods for treating viruses that do not possess an integrase enzyme activity (e.g., see claim 18 wherein anti-viral agents are claimed in general). According to Flint et al., most families of viruses do not employ the use of an integrase enzyme for replication (see Flint, Enquist, Krug, Racaniello and Skalka, "Principles of Virology" ASM press, 2000, pages

750-780; see especially page 764, step 4 wherein the integrase step is shown and compare to the other classes of viruses where no integrase activity is shown such as the picoviruses set forth on pages 750-752 wherein a (-) RNA strand serves as a template for the production of (+) RNA strands without the use of an integrase).

(3 and 5) The state of the prior art and the level of predictability in the art: It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies, as taught by Fahey et al. (Fahey et al., "Status of immune based therapies in HIV infection and AIDS", *Clin. exp. Immunol.* **1992**, *88*, 1-5). The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed pharmaceutical compositions to treat \ HIV infection without undue experimentation.

Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment of HIV infection. For example, Fahey et al. discloses that monoclonal antibody therapies

have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). This is further evidenced by the teachings of Stein et al. who states that the rational development of HIV therapeutics "is limited by our current knowledge of their mechanisms and effects and of the immune system's complex and overlapping activities" (see Stein et al., CID, Vol. 17, 749-771 (1993), page 765, last paragraph). Likewise, Nair et al. state, "There are no drugs for HIV/AIDS in clinical use where the mechanism of action is inhibition of HIV integrase" (e.g., see Nair, "HIV integrase as a target for antiviral chemotherapy" Reviews in medical Virology 2002, 12, pages 179-193, especially pa 179, column 2, noting that HIV integrase "has received much less consideration" than other potential targets such as HIV reverse transcriptase and HIV protease). In addition, Tramontano et al. state that with respect to Applicants' currently claimed integrase inhibitors, in vitro testing don't correlate well with in vivo results (e.g., see Tramontano et al., *Biochemical Pharmacology* **2004**, *67*, 1751-1761, especially page 1752, first full paragraph, "Since integration is an essential requirement for the HIV-1 replication, IN is considered an attractive target for the development of new antiviral therapies ... However, with few exception, the rIN inhibitors identified ... rarely prove to be able to block both the virus replication in cell-based assays and the DNA integration in PIC-based assays ...The striking lack of correlation between the in vitro and in vivo activity of the large majority of anti-IN compounds, irrespectively of the chemical class to which they belong to [4] most likely reflects the inadequacy of the cell-free assays to reproduce the cellular integration process"). Thus, it is clear that the vast majority of

integrase inhibitors do not work. Furthermore, as of Applicants' filing date, there was no reliable way to test their efficacy even if they did.

In addition, a person of skill in the art would not expect an integrase inhibitor to have any effect on the vast majority of known viruses because these viruses do not employ an integrase enzyme in their replication cycles (Flint et al, pages 750-780 comparing replication cycles for various classes of enzymes wherein only the retrovirus family uses the integrase enzyme). Furthermore, a person of skill in the art would not expect an HIV-1 integrase inhibitor to work on an HIV-2 integrase or some other class retrovirus integrase enzyme. Although, molecules like LEDGF that bind more than one type are known (i.e., HIV-1, HIV-2, etc.), this represents the exception rather than the rule (e.g., see Cherepanov et al., Solution structure of the HIV-1 integrase-binding domain in LEDGF/p75, pages 526-532, especially page 520, column 2, last paragraph, "It seems that binding to LEDGF is conserved among the Lentiviridae subfamily of retroviruses and has so far been demonstrated for HIV-1, HIV-2, and FIV INs. In contrast, two other well studied IN-binding partners, integrase-interactor 1 and uracil DNA glycosylase 2 (UNG2), seem HIV-1-specific." Thus, a person of skill in the art wouldn't expect an HIV-1 integrase inhibitor to inhibit a wide class of viral integrase enzymes because these enzymes possess different structures.

Finally, the art of making the claimed salts and hydrates is also unpredictable with respect to pharmaceutical compositions and their methods of use. See for example US 6,864,244 column 1 - column 2; which states: "Salts of acidic and basic compounds can alter or improve the physical properties of the parent compound. These salt forming

agents, however, must be identified empirically by the pharmaceutical chemist since there is no reliable method to predict the influence of a salt species on the behavior of a parent compound in dosage forms. Effective screening techniques, which potentially could simplify the selection process, are unfortunately absent").

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: The specification does not sufficiently establish that the pharmaceutical compositions, mixtures, and methods can be used as claimed. The specification only sets forth evidence in the form of integrase enzyme inhibition studies (e.g., see specification, pages 138 and 140) and there is insufficient evidence that such studies correlate with *in vivo* efficacy in HIV in humans (e.g., see sections 3 and 5 above). Furthermore, no animal data has been provided. Furthermore, Applicants provide no guidance for treating other families of viruses such a picornaviruses, togaviruses, etc. (see above) that do not rely on an integrase enzyme for replication.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445

* n.23 (Fed. Cir. 19991). Here, it is clear from the evidence of Fahey et al., Stein et al., Nair and Tramontano et al., that the ability to treat HIV infection is highly unpredictable and has met with very little success, especially for the currently claimed HIV integrase inhibitors. Applicants have not provided any convincing evidence that their claimed invention is indeed useful as a therapeutic for HIV infection (or any other virus) and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jon D. Epperson/
Primary Examiner, AU 1639